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Quality of life assessment in female patients 2 and 4 years after muscle-derived cell transplants for stress urinary incontinence treatment

Ocena jakości życia kobiet w 2 i 4 lat po transplantacji komórek pochodzących z mięśni w leczeniu wysiłkowego nietrzymania moczu

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Abstract

Introduction: *Regenerative medicine for the treatment of urinary incontinence has become a popular area of focus in the search for therapies for this disease. The paper focused on women's quality of life assessment who were subjected to transplantation of MDSC (autologous muscle derived stem cells) to the urethral sphincter.*

Methods: *The procedure was conducted in 16 female patients who completed the observation stage. Assessment of quality of life before and after the treatment (two and four years post-operation) was conducted based on the validated I-QOL questionnaire (the Polish language version).*

Results: *The questionnaire study showed that autologous cell therapy significantly improves quality of life in female patients suffering from stress urinary incontinence (SUI). The total I-QOL score increased from 49 (SD ± 7.7) before therapy to 77 (SD ± 5.4) two years post-operation. Four years after the procedure, quality of life remained at a higher level than before therapy, although quality of life decreased by several points when compared with the results from the two-year follow-up – 63 (SD ± 7.2). Patients reported significantly less concern related to their ability to reach the toilet to avoid incontinence, improved sleep at night, a higher level of satisfaction with life, and more satisfaction with their sexual lives ($p<0.05$).*

Conclusion: *The MDSC injection procedure for SUI treatment has significant improved quality of life in the majority of our patients in 2 and 4 year follow-up.*

Key words: **quality of life** / **stress urinary incontinence** / **incontinence therapy** / / **muscle derived stem cells** /

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Streszczenie

Cel pracy: *Medycyna regeneracyjna w leczeniu nietrzymania moczu stała się popularnym obszarem zainteresowania w poszukiwaniu metod leczenia tej choroby. Celem niniejszej pracy była ocena jakości życia u kobiet poddanych transplantacji autologicznych dojrzałych komórek pochodzących z mięśni (MDSC) do zwieracza cewki moczowej.*

Materiał i metody: Badanie zostało przeprowadzone w grupie 16 pacjentek, które ukończyły etap obserwacji. Do oceny jakości życia przed i po leczeniu (w dwa i cztery lata po zabiegu) wykorzystano kwestionariusz I-QOL (polska wersja językowa).

Wyniki: *Badania ankietowe wykazało, że terapia z wykorzystaniem autologicznych komórek mięśniowych w znacznym stopniu poprawia jakość życia pacjentek cierpiących z powodu wysiłkowego nietrzymania moczu (WNM). Całkowity wynik I-QOL wzrósł z 49 ± 7,7 (SD) przed leczeniem do 77 (SD ± 5,4) dwa lata po zabiegu. Cztery lata po zabiegu, jakość życia pozostał na poziomie wyższym niż przed leczeniem, chociaż zmniejszyła się o kilka punktów w porównaniu z wynikami z dwóch lat obserwacji - 63 (SD ± 7,2). Pacjentki zgłaszały znacznie mniej objawów związanych z ich możliwością dotarcia do toalety, wyższy poziom zadowolenia z życia i więcej satysfakcji z życia seksualnego (p <0,05).*

Wnioski: *Zastosowana procedura MDSC do leczenia wysiłkowego nietrzymania moczu skutecznie poprawiła jakość życia u większości analizowanych pacjentek po 2 i 4 latach od zbiegu.*

Słowa kluczowe: **jakość życia / wysiłkowe nietrzymanie moczu / terapia nietrzymania moczu / mięśniowe komórki macierzyste /**

Introduction

Statistics show that UI (urinary incontinence) is a major health, social and economic problem [1]. The International Continence Society (ICS) suggested that approximately 8-58% of adult women suffer from UI at some point in their lives [2, 3]. The gold standard in the treatment of SUI (stress urinary incontinence) in woman are the suburethral slings (retropubic or transobturator approach) with up to 90% cure rate for a long time. Despite the high success rates, 10-20% of women stay incontinent. Possible complications of sling are e.g. tape erosion, obstructive voiding and dyspareunia. Patients with structurally damaged sphincter may benefit from an alternative therapy called cell-based therapy[4]. The crucial part of this method is the chosen cell's type or combination of them as well as, the injection technique for proper material placing [5, 6]. Stem cells treatment can differentiate into smooth muscle cells and regenerate the damaged tissue (urethral sphincter). It might be an additional paracrine mechanism of action, by secreting factors that modulate local responses [7]. Regardless of the mechanism of action, every procedure and especially a new one, requires verification through personal subjected both in terms of side effects and long-term effects [8].

To assess the effects of UI on patient quality of life in an objective manner validated versions of questionnaires are used like e.g. I-QOL (Incontinence Quality of Life) which is available in the Polish language [9].

Materials and Methods

The aim of the study was to evaluate patients with SUI (stress urinary incontinence) who were involved into the pilot study previously conducted from 2009 to 2011 in the Clinic of Gynecology and Oncology, JU CM, for MDSC (autologous muscle derived stem cells) urethral sphincter injection. The women participating in the study completed an identical questionnaire to assess their quality of life (I-QOL) prior and two and four years after the procedure with the following results.

The injection procedure tissue material for the study was acquired from deltoid muscle biopsies. Cell culture of the biopsied tissue produced suspended cellular matter, which was applied in the urethral sphincter region circumferential (at 9, 12 and 3 o'clock position) in a group of 16 women. Preoperatively collected general data, medical treatment already used for SUI and past medical history. This trial has gained positive approval from the Jagiellonian University Bioethical Committee. Two years after the procedure, positive results from the therapy were self-reported by 75% of the women as we previously reported [10, 11].

Questionnaire tools for the assessment of quality of life

The I-QOL questionnaire was designed to be used in clinical trials as a disease-specific instrument to measure the impact of UI on the quality of life in men and women experiencing urge, stress, and mixed UI [9]. The questionnaire recommendation has been given a Grade A status, indicating its validity, reliability and responsiveness as established with rigor in several data sets at the Fourth International Incontinence Consultation in 2010 [12].

Statistical methods

The R Package was used for our statistical analysis [13]. The data were analyzed based on Fisher's exact test (some cells in the contingency tables had an expected frequency of five or less). Assessment of the questionnaire data was based on the I-QOL score. The subscale scores were computed by adding each response, subtracting the lowest possible score and dividing that sum by the possible raw score range. The scores were then transformed to present within a range from 0 (maximum problem) to 100 (no problem at all).

Table I. Mean I-QOL scores and standard deviations across all studies; y0 – before the treatment; y2 – two years after the treatment; y4 – four years after the treatment

Period of time	I-QOL Total Score	Avoidance & Limiting Behaviors Score	Psychosocial Impacts Score	Social Embarrassment Score
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
y4	63 ±7.2	67 ±7.01	64 ±5.5	55 ±4.7
y2	77 ±5.4	78 ±4.7	78 ±4.9	73 ±6.1
y0	49 ±7.7	47 ±8.15	53 ±7.5	46 ±5.6

Table II. Summary of questionnaire responses (I-QOL) related to avoidance and limiting behavior to assess the quality of life of patients before (y0) and after cell transplantation (y2 –2 years after treatment, y4 –4 years after treatment).

	I-QOL questions		I-QOL score			Fisher test; p-value		
			y0	y2	y4	y0-y2	y0-y4	y2-y4
Avoidance and Limiting Behavior (ALB)	1	I worry about not being able to get to the toilet on time.	42	75	72	0.008863	0.04825	0.8417
	2	I worry about coughing or sneezing because of my urinary problems or incontinence.	45	83	66	0.0001446	0.05164	0.2161
	3	I have to be careful standing up after I've been sitting down because of my urinary problems or incontinence.	58	83	77	0.2967	0.6743	0.9155
	4	I worry about where toilets are in new places.	38	78	59	0.0007211	0.1179	0.2569
	10	It's important for me to make frequent trips to the toilet.	38	73	58	0.004844	0.1753	0.5563
	11	Because of my urinary problems or incontinence, it's important to plan every detail in advance.	59	84	70	0.04821	0.08051	0.5579
	13	I have a hard time getting a good night of sleep because of my urinary problems or incontinence.	50	78	73	0.04571	0.01515	1
	20	I have to watch what or how much I drink because of my urinary problems or incontinence.	48	72	61	0.02683	0.4244	0.4748

Table III. Summary of questionnaire responses (I-QOL) for the group of questions related to psychosocial impacts to assess the quality of life of female patients before (y0) and after cell transplantation (y2 - after 2 years, y4 - after 4 years).

	I-QOL questions		I-QOL score			Fisher test; p-value		
			y0	y2	y4	y0-y2	y0-y4	y2-y4
Psychosocial Impacts (PS)	5	I feel depressed because of my urinary problems or incontinence.	67	83	64	0.1186	0.5132	0.6177
	6	Because of my urinary problems or incontinence, I don't feel free to leave my home for long periods of time.	59	86	72	0.03931	0.05461	0.5857
	7	I feel frustrated because my urinary problems or incontinence prevent me from doing what I want.	53	77	64	0.05104	0.06639	0.5857
	9	My urinary problems or incontinence are always on my mind.	44	75	59	0.005987	0.06639	0.5647
	15	My urinary problems or incontinence make me feel like I'm not a healthy person.	47	72	61	0.2503	0.587	0.8921
	16	My urinary problems or incontinence make me feel helpless.	48	73	59	0.2503	0.07039	0.7938
	17	I get less enjoyment out of life because of my urinary problems or incontinence.	47	75	64	0.01035	0.05359	0.7848
	21	My urinary problems or incontinence limit my choice of clothing.	56	80	58	0.01371	0.4011	0.4202
	22	I worry about having sex because of my urinary problems or incontinence.	59	83	73	0.007611	0.01848	0.7888

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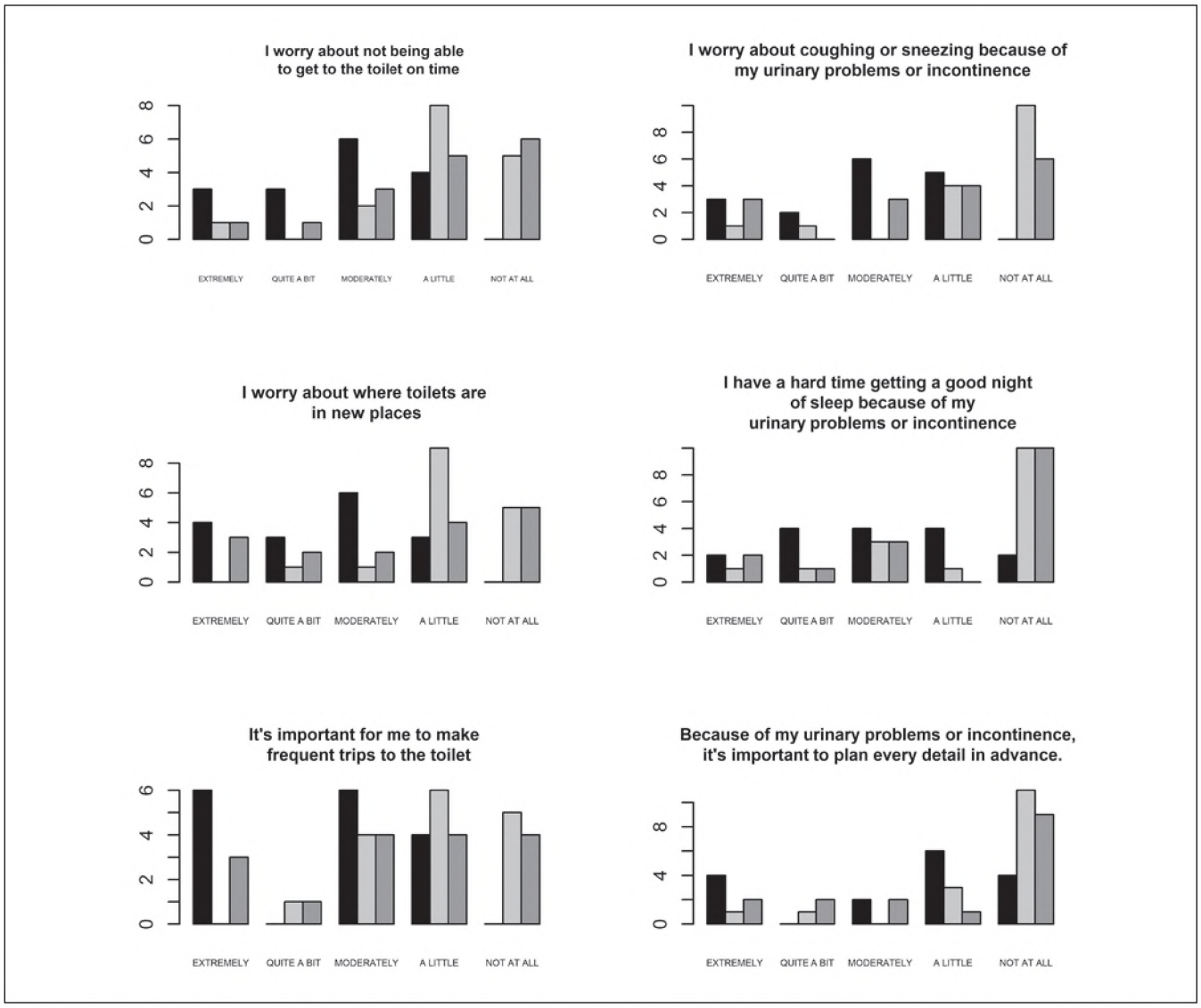

Figure 1. Incidence of patients responding to the questions related to avoidance and limiting behavior. The charts refer to data for which the result of the statistical study was significant ($p<0.05$). y0 – black (before treatment); y2 – light gray (2 years after treatment); y4 – gray (4 years after treatment).

Results

I-QOL questionnaire interviews were related to avoidance and limiting behavior (ALB), psychosocial impact (PS) and social embarrassment (SE). Comparison of the answers of the patients showed that the comprehensive I-QOL score (determining the level of quality of life on a scale of 0-100) was significantly improved. Two years after the procedure, I-QOL increased from 49 to 77. The quality of life decreased by four years post-procedure to 63, although the average quality of life score at this time point remained higher than pre-procedure (Table I).

The greatest increase among all quality of life measures was observed for avoidance and limiting behavior (ALB) at two years (y2) after the treatment. ALB scores were 31 points higher at y2 than before the treatment (y0). ALB scores showed the greatest improvement at the four-year (y4) time point as well, as ALB scores remained higher by 20 points when compared with pre-treatment (y0) values.

Social embarrassment (SE) scores showed the lowest degree of improvement over the course of the study. The average SE score two years after the procedure was 73, which was higher than the average SE score before the treatment (y0) by 27 points. However, the decrease in the average SE score between y2 and y4 was 18 points, which represents the strongest decrease of all quality of life subcategories (ALB, PS and SE). These results may suggest that failures related to treating SUI are most apparent in deterioration in the quality of life related to SE.

Avoidance and Limiting Behavior (ALB)

Patient responses after treatment indicated a clear decrease in the fear of not reaching the toilet in time and in the fear that sneezing or coughing may cause incontinence. A decrease in these fears was recorded 2 and 4 years after the treatment relative to patient responses before the procedure (questions 1 and 2 in Table II). Anxiety related to constantly thinking about the nearest bathroom also showed a significant decrease (question 4, Table

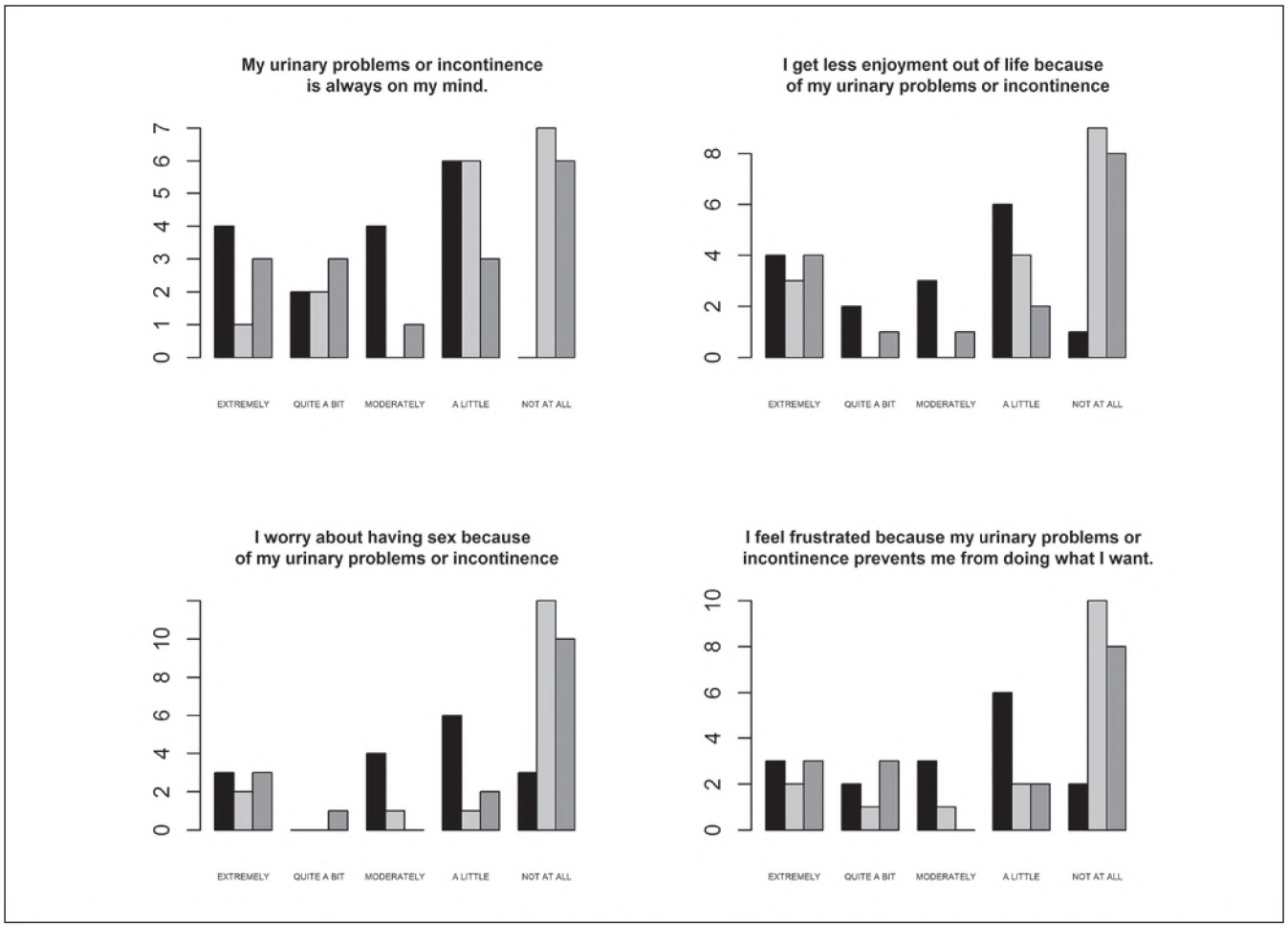

Figure 2. Incidence of female patients responding to questions related to psychosocial impacts. The charts refer to data for which the result of the statistical study was significant ($p<0.05$). y0 – black (before treatment); y2 – light gray (2 years after treatment); y4 – gray (4 years after treatment).

II). Despite the small sample size, a positive trend was obvious (increased quality of life in patients) after the procedure (Figure 1). However, we note that the I-QOL quality of life coefficient decreased between two years (y2) and four years (y4) after the procedure.

No correlation was observed between the effects of the therapeutic procedure and either the required effort to avoid urinating while standing up or patient awareness of what they drink and in what quantity ($p>0.05$; Table II).

Psychosocial Impacts (PS)

In women who experience UI, in addition to the physiological inconvenience, some psychological symptoms were reported that affected the physical and mental condition of the patients, their self-assessment and their ability to function in life. Many female UI patients experience depression and frustration. Constantly thinking about UI causes continuous awareness and pressure, which can result in fear of sexual activity. Patients often indicate their helplessness and a general lack of joy in life due to SUI.

The effects of MDC therapy indicate that reduction or elimination of the physiological problems related to UI significantly increases self-assessment in female patients in many areas of psychology (Table III). Interestingly, the positive effects decreased slightly over time. Four years after the procedure, fewer patients stated positive change related to UI (Table III, Figure 2).

In most cases, patients with persistent thoughts about UI stated that after the cell therapy, they thought less constantly about their condition (Figure 2). Similar results were observed with respect to questions about the general satisfaction with life of the patients. Patients mostly reported an increase in their ability to function and a decrease in frustration. In addition, the sexual lives of the patients improved (Figure 2).

Patient responses to some questions did not change statistically significantly regardless of the time of the questionnaire (before therapy, two years after and four years after). For the question about feeling depressed, the patients depression due to their illness. Similar results were obtained with respect to the question about feeling helpless. Interestingly, each response group (corresponding to EXTREMELY, QUITE A BIT, MODERATELY, A LITTLE and NOT AT ALL) featured similar proportions of patients, even though the largest group of responses was observed in patients who did not feel depressed or helpless due to their ailment (Table III).

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Table IV. Summary of questionnaire responses (I-QOL) corresponding to social embarrassment questions to assess the quality of life of female patients before (y0) and after cell transplantation (y2 - 2 years after treatment, y4 - 4 years after treatment).

	I-QOL questions		I-QOL score			Fisher test; p-value		
			y0	y2	y4	y0-y2	y0-y4	y2-y4
Social Embarrassment (SE)	8	I worry about others smelling urine on me.	48	78	58	0.07711	0.5374	0.4114
	12	I worry about my urinary problems or incontinence getting worse as I grow older.	41	63	47	0.3527	0.2469	0.5608
	14	I worry about being embarrassed or humiliated because of my urinary problems or incontinence	55	78	58	0.3735	0.5988	0.5413
	18	I worry about wetting myself.	47	72	58	0.03846	0.08956	0.3501
	19	I feel like I have no control over my bladder.	42	72	56	0.02707	0.05051	0.2773

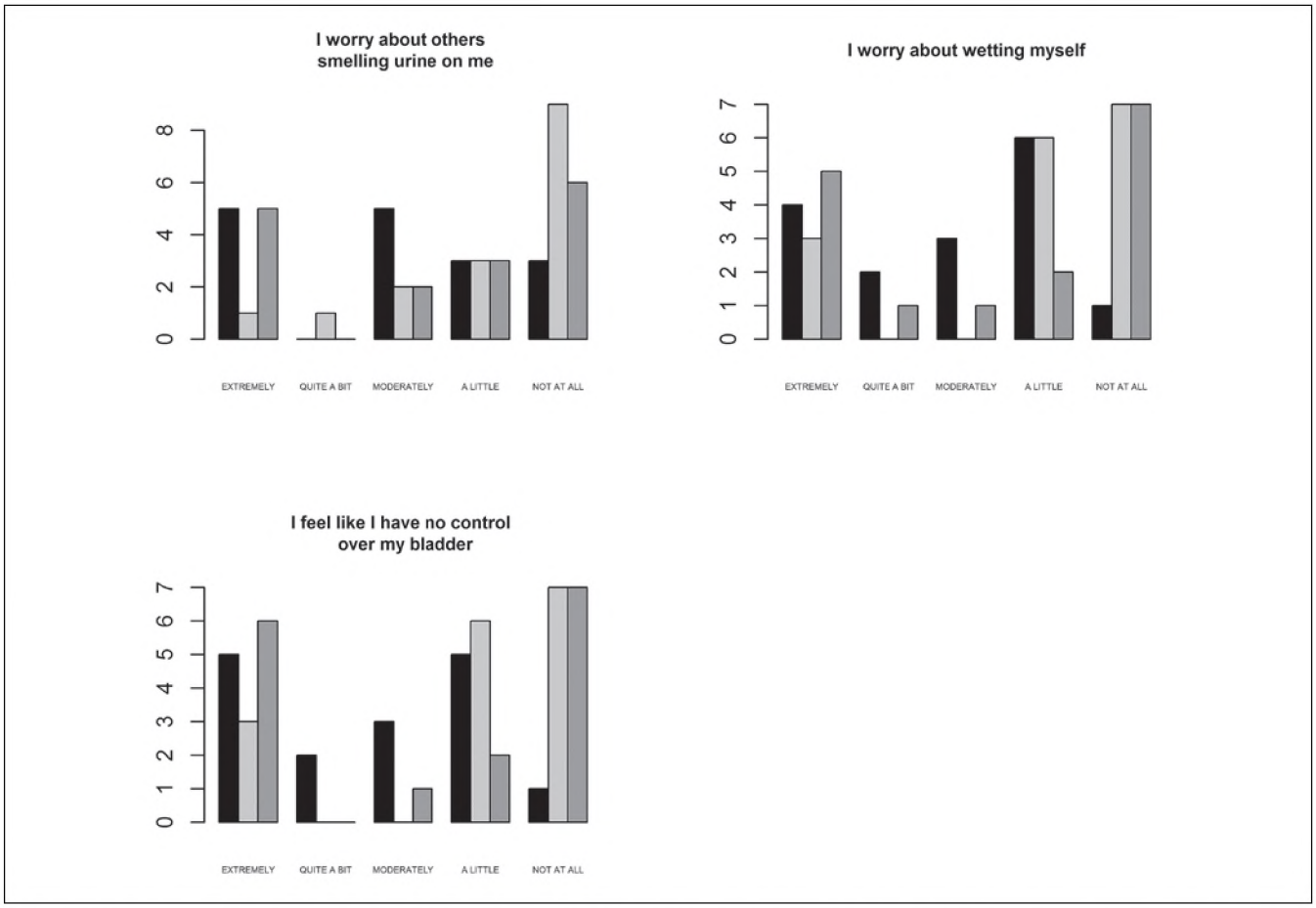

Figure 3. Incidence of female patients responding to the questions related to social embarrassment (SE). The charts refer to data for which the results of the statistical study were significant at two years after the treatment ($p<0.05$). y0 – black (before treatment); y2 – light gray (2 years after treatment); y4 – gray (4 years after treatment).

Social Embarrassment (SE)

This study showed that stress involved in UI is to some extent continuous (despite positive therapeutic effects). For example, patients remained concerned that their UI problem would recur after some time (Table IV).

The patients expressed the fear that others may smell the odor of urine as well as a fear of their incontinence and a lack of control over their bladder (Figure 3).

Discussion

Treatment of incontinence is different from other fields of health care in that health related quality of life is seen as the central goal, not as a secondary outcome. For objective evaluation of quality of life assessment, different validated questionnaires are used. They should be translated into the language of the country like e.g. I-QOL [9]. Assessment of the clinical condition and the questionnaire results prior and 2 and 4 years after the MDC treatment was administered in women with stress UI indicates that the therapeutic result is durable in the

majority of the included patients. Importantly, improvements in patient function were observed in areas such as social life, family life, job/work, intimate relationships, daily activities, household activities, recreation and travel, mental health, physical health and anxiety/depression. The psychological condition of the patients significantly improved. We suspect that improvement in patient comfort and an increase in the time needed to reach a toilet without experiencing incontinence may be factors in determining social behavior of the patients. With these improvements, the patients reported feeling more self-confident. None of the women subjected to the treatment reported negative feedback with respect to the therapy itself, even if total control over urination was not gained. Moreover, in response to the question about whether the patients would participate in another round of the therapy, they declared a willingness to continue their treatment. However, it is difficult to compare results across studies, Carr et al. demonstrated autologous muscle derived cells (AMDC) dose range injection safety with the quality of life assessment. Mean IIQ-7 scores for low and high dose groups did not differ significantly at baseline or 18 months. Mean UDI-6 scores for patients in low and high dose groups differed significantly from baseline to 18 months [14]. Blaganje et al. injected autologous muscle-derived stem cells in 38 women with SUI. Initially the women were treated with electrical stimulation alone for 6 weeks. Then the stem cells were injected, and another 6 weeks of electrical stimulation were given. At the end of this 6-week period, 5 women were cured and 29 improved. Unfortunately, there was no control group [15].

So far, no randomized controlled data are available, nor are there any comparison assessment suburethral sling procedures with MDSC treatment. Dosage of cells injected, number of injection and the method of delivery are other factors that need to be addressed in a future study. Nonetheless, all studies published to date report low rates of operative morbidity for intrasphincter injection of autologous muscle cells.

Conclusion

The MDSC injection procedure for SUI treatment has significant improved quality of life in the majority of our patients in 2 and 4 year follow-up.

Ethical approval: *All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its amendments or comparable ethical standards.*

Informed consent : *Informed consent was obtained.*

Oświadczenie autorów:

1. Klaudia Stangel-Wójcikiewicz – autor koncepcji i założeń pracy, przygotowanie manuskryptu i piśmiennictwa – autor zgłaszający i odpowiedzialny za manuskrypt.
2. Monika Piwowar – zebranie materiału, analiza statystyczna wyników, przygotowanie manuskryptu.
3. Robert Jach – autor założeń pracy, analizy i interpretacji wyników, przygotowanie, korekta i akceptacja ostatecznego kształtu manuskryptu.
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